Letters to the Editor

Additional Rheumatologic Tests Critical in Patients with Systemic Sclerosis

Original Article: Rheumatologic Tests: A Primer for Family Physicians

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To the Editor: Two important pieces of information are missing in this article's brief discussion of systemic sclerosis (SSc) testing that could lead to an incorrect diagnosis and potential negative consequences for the patient.

The American College of Rheumatology recommends an indirect immunofluorescence assay (IFA) for initial antinuclear antibody (ANA) testing.[1] The article notes that ANA testing with enzyme-linked immunosorbent assay is less accurate than with IFA. However, IFA testing is critical in patients with SSc. A 2011 study noted that multiplex ANA testing in patients with SSc has a 43% false-negative rate.[2] The primary reason is that enzyme-linked immunosorbent assay and multiplex ANA testing panels include only one to three of the 10 currently identified SSc-specific antibodies. No standard ANA screening panel that I am aware of includes testing for RNA polymerase III antibody, the third most common SSc-related antibody, which is present in 20% of patients wih SSc.[3] If the ANA screening panel includes Scl 70 (topoisomerase) as the only SSc-specific antibody, the false-negative rate can be as high as 80%,[3] potentially delaying a correct diagnosis for years.

Dr. Ali's article indicates that patients with a positive ANA titer (by IFA) should undergo follow-up antibody testing. It recommends testing for anti-Scl 70 and anticentromere antibodies, which is correct. However, it neglects to mention RNA polymerase III antibodies. This diffuse scleroderma-related antibody is as common as the anti-Scl 70 antibody in patients with SSc, and it is associated with a high risk of developing scleroderma renal crisis. Patients with this antibody must monitor their blood pressure daily for a sudden spike that persists for even a few hours. This is a potentially life-threatening complication, so missing this antibody in initial screening can be very dangerous.

It may also be worth noting that in addition to the three common SSc-related antibodies (anticentromere, anti-Scl 70, and anti-RNA polymerase [RNAP] III), there are five rare antibodies for which commercial testing is available if test results for the more common antibodies are negative. One of these (antiribonucleoprotein U1 antibody) is associated with mixed connective tissue disease and was discussed in Dr. Ali's article. The others are anti-Th/To ribonucleoprotein, anti-U3 ribonucleoprotein, anti-PM/Scl, and anti-Ku antibodies. The latter two are associated with scleroderma-myositis overlap syndromes.

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In Reply: Thank you for your interest in my article. You point out the need for IFA testing in patients with suspected scleroderma because of the high false-negative rate of multiplex ANA testing. This test is commonly used in commercial laboratories and involves coating beads with multiple antigens, then incubating them with the patient's diluted serum. Because many

autoantibodies can be detected simultaneously, this results in more efficient handling of large samples. I agree that solid-phase testing (e.g., multiplex beads) can be inadequate when screening for scleroderma and myositis, and may result in false reassurance. This is especially problematic when the test result is negative and the patient has vague symptoms. The American College of Rheumatology recommends that laboratories specify the methods used to detect ANAs when reporting results.[1] Physicians should account for the pretest probability of disease when interpreting test results and be aware of both the technique and limitations of laboratory testing.

You also point out that patients with suspected scleroderma should undergo testing for anti-RNAP III because these antibodies are as common as anti-Scl 70. Anti-RNAP III has not traditionally been used as a screening tool; although it is highly specific for scleroderma, it is detected in only 11% to 24% of patients with the disease.[2,3] Despite this low sensitivity, anti-RNAP III is now included in the American College of Rheumatology/European League Against Rheumatism criteria for scleroderma[4] and is associated with the development of diffuse scleroderma, malignancy, and renal crisis. I agree that in patients with suspected

scleroderma who have a positive ANA test result, additional testing should also include anti-RNAP III. The five other rare autoantibodies associated with scleroderma were not mentioned in my article because these are out of the scope of what is expected of most primary care physicians.
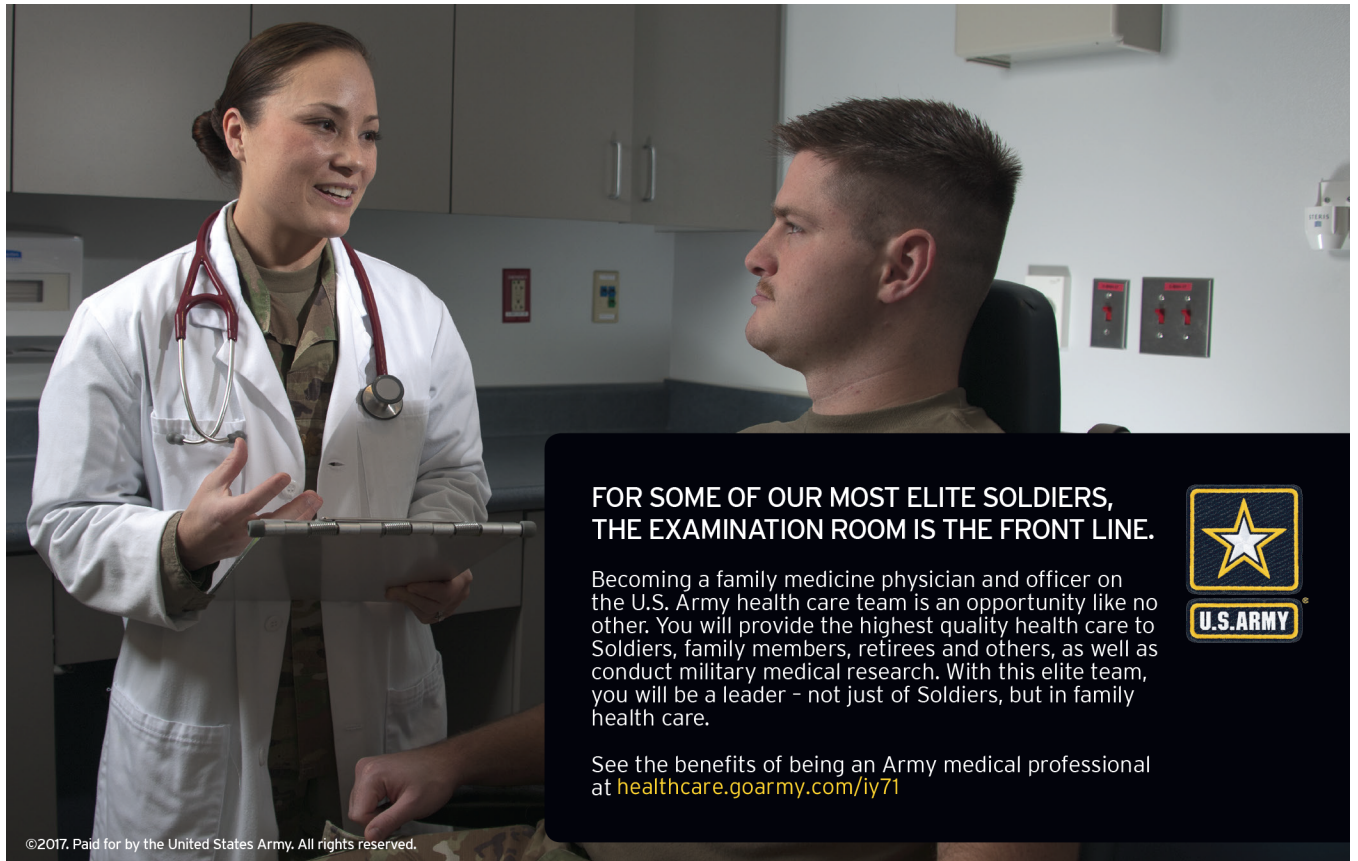
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